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Exploration of a Symptoms Experience in People with Obesity-Related NAFLD

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Abstract

Background—Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition strongly associated with obesity that can result in premature death. Little is known about a symptoms experience in this progressive disease, preventing health care providers from intervening in the early stages.

Purpose—This study explicated symptoms in persons with NAFLD at higher risk of disease progression defined as the presence of one or two copies of the *PNPLA3* gene, (rs738409)-G allele.

Method—Guided by the Symptoms Experience Model, 42 persons >21 years of age with diagnosed NAFLD were recruited from Western Michigan specialty offices in this cross-sectional descriptive study design. The Memorial Symptom Assessment Scale was used to measure the symptoms experience.

Discussion—Participants (97%) experienced 1 or more symptoms (average number of symptoms 12.02, SD 8.817). There was no statistically significant relationship between symptoms and the *PNPLA3* (rs738409) variants. Significant predictors of mean frequency, severity and distress of symptoms [TMSAS] ($F=2.609$; $df_1=15$, $df_2=25$; $p=.016$) were identified.

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Conclusion—Persons with NAFLD experience an average of 12 symptoms.

Keywords

PNPLA3; NAFLD; Symptoms Experience

Obesity-related nonalcoholic fatty liver disease (NAFLD) is a rapidly growing worldwide health concern (Houghton-Rahrig et al., 2011). In the United States alone, 30 to 70 million persons have NAFLD (Adams, Lymp, et al., 2005; American Liver Foundation, 2007; Angulo, 2007; Chan et al., 2007; Choudhury & Sanyal, 2004). Experts estimate that by the year 2030, the prevalence of obesity-related NAFLD will reach epidemic proportions in the U.S. (Younossi et al., 2011). NAFLD, defined as fatty deposits comprising 5% or more of the total liver weight, may progress from simple fatty liver disease to end stage liver disease resulting in premature death (Angulo, 2007; Kistler et al, 2010). In most cases, NAFLD is not discovered until later stages of the disease (Adams, Lymp, et al., 2005). However, if NAFLD is found early, progression can be halted or even reversed through implementation of weight loss strategies (Dixon, Bhathal, Hughes, & O'Brien, 2004; Mummadi, Kasturi, Chennareddygar, & Sood, 2008; Promrat et al., 2010).

Background and Significance

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is strongly associated with obesity, metabolic syndrome and insulin resistance and its incidence is thought to parallel the obesity epidemic (Adler & Schaffner, 1979; Vernon, Baranova, & Younossi, 2011; Younossi et al., 2011). NAFLD can progress from simple fatty liver disease to an inflammatory stage called Nonalcoholic Steatohepatitis (NASH), with or without liver fibrosis to liver cirrhosis followed by liver failure or liver cancer/liver failure resulting in premature death (Adams, Angulo, & Lindor, 2005; Angulo, 2007).

NAFLD is a worldwide health concern. In the U.S., NAFLD is most common in Hispanics, followed by whites and African Americans (Browning et al., 2004; Victor et al., 2004). Further study is needed to determine the incidence of NAFLD in the American Indian and Alaskan Native populations (Bialek et al., 2008; Fischer, Bialek, Homan, Livingston, & McMahon, 2009; Houghton-Rahrig et al., 2011). In the U.S., 1 in every 3 adults and 1 in 10 children have NAFLD (Angulo, 2007a). There is an equal prevalence in male and female adults, but a slightly higher prevalence in young males and white adult males (American Liver Foundation, 2007; Chang et al., 2008; Houghton-Rahrig et al., 2011). Sixty-seven to 78% of persons with a BMI of 30 or greater have NAFLD (Williams et al., 2011).

Severity of disease marker - *PNPLA3* gene

While liver biopsy is the gold standard for confirmation, grading, and staging of NAFLD (Yan, Durazo, Tong, & Hong, 2007), only a small percentage of persons have liver biopsies due to the risk of bleeding (Caldwell, Argo, & Al-Osaimi, 2012). Liver function tests, such as ALT and AST, may be elevated in persons with NAFLD triggering an evaluation for NAFLD. Many times, patients may have NAFLD as noted by imaging, but may not have elevated enzymes. For example, in a study of persons with diabetes in Italy, 70% had NAFLD, but did not have elevated liver enzymes (Targher et al., 2007). In addition, imaging modalities can identify persons with NAFLD, but are not sensitive enough to stage and grade disease (Mehta, Thomas, Bell, Johnston, & Taylor-Robinson, 2008). Taken together, no known biomarkers were available at the initiation of this study for grading and staging of disease.

In light of the lack of clinical biomarkers, research to examine potential DNA biomarkers of disease risk and progression are ongoing. For example, a DNA polymorphism (rs738409) in the *PNPLA3* (patatin-like phospholipase domain containing 3) gene was found to be strongly associated with NAFLD (Romeo et al., 2010; Sookoian et al., 2009). *PNPLA3* encodes a protein called adiponutrin, a triacylglycerol lipase that mediates triacylglycerol hydrolysis in adipocytes. This particular *PNPLA3* gene variant (rs738409) is a nonsynonymous polymorphism; that is, it is a substitution of the normally occurring cytosine to guanine that results in an amino acid change from isoleucine to methionine (NCBI Entrez Gene, 2010). Subsequently, the amino acid change is thought to inhibit the normal breakdown of triglycerides resulting in an increased storage of triglyceride in the hepatocytes (He et al., 2010).

Recent studies such as the Dallas Heart Study suggest that the *PNPLA3* gene, (rs738409)-G allele, is strongly associated with NAFLD ($p=5.9 \times 10^{-10}$), and this association is more significant after adjusting for BMI, diabetes, alcohol use and ancestry, ($p=7.0 \times 10^{-14}$). Further, the rs738409-G allele is associated with disease progression and severity of disease (Kotronen et al., 2009; Romeo et al., 2008a; Romeo et al., 2010; Sookoian et al., 2009; Tian, Stokowski, Kershenovich, Ballinger, & Hinds, 2010a). In fact, there is a dose effect in that those persons with two copies of the rs738409-G allele were more likely to have advanced disease than those persons with one copy or no copies of the G allele (Valenti et al., 2010). In addition, the *PNPLA3* gene polymorphism was also found to be associated with elevated alanine aminotransferase serum levels, a liver function test associated with liver injury in Hispanics (Tian et al., 2010). Interestingly, Hispanics have a higher prevalence of NAFLD (Browning et al., 2004).

Conceptual Framework

An adapted Symptoms Experience Model (Armstrong, 2003) guided this study (Adapted with permission from “Symptoms Experience: A Concept Analysis” by T.S. Armstrong, 2003, *Oncology Nursing Forum*, 28(7), p. 603. Copyright 2003 by ONS). Armstrong defines symptoms experience as the “perception of the frequency, intensity and distress of symptoms as they are produced and expressed” (Armstrong, 2003) [p.603]. An important aspect of the Symptoms Experience Model for the purpose of this study is the proposed interaction of antecedents, such as demographic, disease and individual characteristics, to influence the symptom experience. In this study, genetic influences such as the *PNPLA3* (rs738409) polymorphism are examined as an antecedent factor that may influence disease progression. Symptom presence, frequency, intensity and distress are perceived by the individual. Symptoms may occur in clusters and have a catalytic, multiplicative effect upon other symptoms (Armstrong, 2003; Dodd, Miaskowski, & Paul, 2001; Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The Memorial Symptom Assessment Scale (Portenoy et al., 1994), provides a multi-symptom measure of the symptom experience in this study, recognizing the likely complex nature of symptoms in persons with NAFLD. The outcome of the dissertation study from which these two out of four aims for this paper was derived, was health-related quality of life. However, the symptoms experience was the outcome for the two aims used for this analysis. The adapted version of Armstrong's Symptoms Experience Model used in this study did not include the situational and existential meaning of symptoms.

Scientific Gap

Currently, little is known about the symptoms experience throughout the disease trajectory in persons with obesity-related NAFLD (Houghton-Rahrig et al., 2011; Salt, 2004). A lack of knowledge about a potential symptoms experience in this population prevents health care providers from intervening to prevent, halt or reverse the disease, both in the early stages of

NAFLD and throughout the disease course (Houghton-Rahrig et al., 2011). NAFLD is more apt to improve or resolve when treated in the early stages of the disease (Mummadi et al., 2008).

Purpose

The purpose of this study was to identify and describe symptoms in persons with NAFLD (Houghton-Rahrig et al., 2011). The first aim of this study was to identify the presence of symptoms in persons with NAFLD, comparing those at higher risk of disease progression based on the presence of one or two copies of the *PNPLA3* (rs738409)-G allele variant compared to those at lower risk of disease progression [no copies of the *PNPLA3* rs738409-G allele] (Houghton-Rahrig et al., 2011). Once symptoms were determined, our second aim was to compare the extent to which the frequency, intensity, and distress of symptoms in persons with NAFLD differed between those at higher risk of disease progression based on the presence of one or two copies of the *PNPLA3* (rs738409)-G variant compared to those at lower risk of disease progression [no copies of the *PNPLA3* rs738409-G allele] (Houghton-Rahrig et al., 2011).

Methods

Study Design and Sample

Forty-two participants with NAFLD, diagnosed by imaging (such as ultrasound, MRI or CT) as recorded in their medical record, were enrolled in this correlational, cross-sectional study. NAFLD staging by liver biopsy was only available for 33% of participants ($n=14$). Of these 14 participants, 4 had NASH without fibrosis, 5 had NASH with stage 0-1 fibrosis and 5 had NASH with stage 3-4 fibrosis. That is, 9 were in the early stages of disease, and 5 were in the later stage of NAFLD. Participants were recruited from two offices; a gastroenterology office, and a surgical office where gastric banding and general surgery are performed. One participant who was not a patient at either of these offices contacted the Principal Investigator (PI) asking to be included in this study.

Procedures

Participants with diagnosed NAFLD were recruited during office appointments. The medical assistant provided a flyer about the study to eligible patients and asked if they would be interested in participating. If interested, the patients signed a Patient Authorization for Disclosure of Health Information for Research form to allow the PI to talk with the patient. Once signed, the PI met with the potential participants to answer any questions and obtain consent to participate in the study. The PI provided a questionnaire, helped the participant provide a saliva sample, and obtained waist/hip circumference measurements. A medical record audit was also conducted to obtain medical/surgical history, medications, laboratory values, and NAFLD staging and grading results from liver biopsies, if available. Medications were those prescribed as noted in the chart. Serum AST and ALT results were obtained from the chart audit if the patient had elevated liver enzymes during recruitment or in the past as these levels may fluctuate as participants lose and gain weight (Burza et al., 2013).

Instruments

The Charlson Comorbidity Index was used to “count” and control for comorbid conditions in the multiple linear modeling analyses (Charlson, Pompei, Alex, & MacKenzie, 1987). The Memorial Symptom Assessment Scale (MSAS) measured the presence, frequency, intensity and distress of 32 symptoms allowing participants to write in symptoms as well

(Portenoy et al., 1994). Four subscales of the MSAS were used to measure symptom attributes:

The Total Memorial Symptom Scale (TMAS) measured the sum of frequency (if applicable), severity (intensity), and distress, averaging the sum of each of the 32 symptoms; averaged using the total number of symptoms. The Memorial Symptom Assessment Scale – Global Distress Index (MSAS-GDI) measured overall distress from the average frequency of 4 psychological symptoms (feeling sad, worrying, feeling irritable and feeling nervous,) and distress of seven physical symptoms [lack of appetite, lack of energy, pain, feeling drowsy, constipation and dry mouth]. The Memorial Symptoms Assessment Physical Scale (MSAS-PHYS) is the average of the frequency, severity (intensity) and distress of 12 physical symptoms [lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated and dizziness]. Finally, the MSAS-PSYCH is the average of the frequency, severity (intensity) and distress of six psychological symptoms [feeling sad, worrying, feeling irritable, feeling nervous, difficulty sleeping and difficulty concentrating] (Portenoy et al., 1994) [p. 1336].

Oragene® DNA Self-Collection Kits were used to obtain saliva samples for DNA extraction. Genotyping of rs738409 was completed using the Taqman® PCR (Applied Biosystems, Carlsbad, CA). Validity and reliability of instruments are reported in Table 1.

Data Analysis

Data were analyzed using PASW 17 software (SPSS, Inc., Chicago, IL). Participants' data were stratified into two groups, 1) persons at higher risk of disease progression as defined by the presence of one or two copies of the *PNPLA3* (rs738409)-G allele and 2) persons at lower risk of disease progression defined as no copies of the *PNPLA3* (rs738409)-G allele (Houghton-Rahrig et al., 2011). Individual symptoms (the dependent variables) were grouped into dichotomous variables (present or absent). Likewise, the *PNPLA3* gene, (rs738409) variant was grouped into dichotomous variables [presence or absence of G-allele] (Houghton-Rahrig et al., 2011). To determine the likelihood of the presence of one or two copies *PNPLA3* (rs738409)-G allele with the presence of each symptoms, Odds ratios and Fisher's exact tests were used (Houghton-Rahrig et al., 2011). Multiple linear regression was used to identify predictors of symptom frequency, intensity and distress.

Results

Descriptive Statistics

The majority of participants were white females, employed with a high school education. Nearly forty-three percent of participants had no copies of the *PNPLA3* (rs738409)-G allele leaving 57.2% with one or two copies of the G-allele. Body Mass Index (BMI) was the sole statistically significant difference between the two genotype groups. Medications that participants were prescribed were similar between genotype groups such as vitamins, antidepressants, antihypertensives, and antihyperglycemics. Table 2 provides descriptive statistics of the demographic, disease and individual characteristics that were used in the analysis of this study.

Symptoms and the *PNPLA3* gene, (rs738409) genotype

We hypothesized that persons at higher risk of disease progression as evidenced by the presence of one or two copies of the *PNPLA3* gene, (rs738409)-G allele may experience more symptoms than persons with no copies of the G-allele. In this study, persons with NAFLD experienced 12 symptoms on average (S.D.8.81, range 0-34). Ninety-seven percent

of persons experienced one or more symptoms. However, there was no significant relationship between the presence of symptoms and the *PNPLA3* (rs738409) genotype. Persons with no copies of the *PNPLA3* (rs738409)-G allele had a mean of 11.67, (SE=1.72) symptoms compared to persons with one to two copies of the *PNPLA3* (rs738409)-G allele (M=12.29, SE = 2.24). In addition, there was no significant difference between BMI and the number of symptoms experience by participants in this study [$F = 1.122$, $df1 = 1$, $df2 = 40$, $p = .296$] (Houghton-Rahrig et al., 2011). There was also no difference in the mean number of symptoms between those with a BMI less than 30 (M=11.86) compared to persons with a BMI of 30 or greater [M=12.06] (Houghton-Rahrig et al., 2011). See Table 3 for a comparison of symptom frequencies according to *PNPLA3* (rs738409)-genotype.

Symptom Frequency, Intensity and Distress

We also hypothesized that persons at higher risk of disease progression, as evidenced by the presence of one or two copies of the *PNPLA3* (rs738409)-G allele, would have more symptom intensity, frequency and/or distress than those persons at lower risk of disease progression, i.e. without the *PNPLA3* (rs738409)-G allele. Variables used in the following multiple linear regression models included the demographic, disease, and individual characteristics highlighted in Table 2. The enter method of PASW 17 (SPSS Inc., Chicago, IL) was used in all multiple linear regression analyses. The *PNPLA3* gene variant was not a significant predictor of the frequency, intensity and distress of symptoms as measured by the TMAS, MSAS-GDI, MSAS-PHYS or MSAS-PSYCH subscales as hypothesized. However, “nonwhite” race was a significant predictor of all symptom distress. Unemployment was a significant predictor of global symptom distress and psychological symptoms, whereas, health knowledge of NAFLD prior to recruitment into the study was a significant predictor of physical symptoms (See Table 4).

Discussion

Demographics

Race is a predictor of the total of all symptoms, distress of symptoms, physical and psychological symptoms in this study. Participants in this study who identified their race/ethnicity as Hispanic or Multiracial (“nonwhite” group) experienced more symptoms (M=22.83) compared to persons who identified their race/ethnicity as Caucasian (“white” group) with a mean of 10.22 symptoms [$p=.001$] (Houghton-Rahrig et al., 2011). These findings are congruent, in some respect, to prior observations that Hispanics have a higher incidence of NAFLD and are at higher risk of disease progression based on the presence of the *PNPLA3* (rs738409)-G allele (Browning et al., 2004; Sookoian et al., 2009; Tian, Stokowski, Kershenovich, Ballinger, & Hinds, 2010b; Valenti et al., 2010). The mechanism behind these observations is not clear.

Persons who were unemployed, disabled or retired reported higher distress scores from than those who were employed and those with higher psychological subscale scores. The MSAS-GDI measured the frequency of psychological symptoms of feeling sad, worrying, feeling irritable and feeling nervous. The MSAS-GDI also included the distress of the following physical symptoms such as lack of appetite, lack of energy, pain, feeling drowsy, constipation, and dry mouth (Portenoy et al., 1994).

Disease Characteristics

No disease characteristics were predictors of symptoms in this study. While more symptoms were reported in persons with one or two copies of the *PNPLA3* (rs738409)-G allele as noted in Table 4, the relationship was not statistically significant. Further, the *PNPLA3* (rs738409)-G allele was not a contributor to the symptoms experience as noted in the MSAS

subscales listed in Table 4. Interestingly, persons with no copies of the *PNPLA3* (rs738409)-G allele had statistically higher BMI values than persons with one or two copies of the *PNPLA3* (rs738409)-G allele as noted in Table 1. This may represent a need to increase our sample size as BMI is similar between *PNPLA3* (rs738409) genotype groups in other studies (Romeo et al., 2008; Valenti et al., 2010). Additional participants are needed to increase the power in this study for a more accurate evaluation. In future studies, evaluation with a larger sample size may be beneficial.

Individual Characteristics

Prior knowledge of NAFLD prior to enrollment in the study was a predictor of physical symptoms. In this study, persons who had prior knowledge of the presence of NAFLD had more symptoms ($M=13.75$, $SE=1.56$) compared to those who learned about their diagnosis of NAFLD on the day that they were enrolled in the study [$M=8.57$ symptoms, $SE=2.45$] (Houghton-Rahrig et al., 2011). Hegyvary notes that symptoms are “red flags” of threats to health (Hegyvary, 1993). Perhaps persons aware that they had NAFLD prior to the study were looking for symptoms to be present or were more aware of symptoms. Further study is needed in this area.

Outcome of Symptoms Experience

In contrast to conventional wisdom that NAFLD is largely asymptomatic, findings from this study suggest that symptoms exist and are, in fact, prevalent in persons with NAFLD. Very few studies are available that measure symptoms in persons with NAFLD. Nonetheless, our findings are consistent with a study of children in NAFLD (Kistler et al., 2010), who also identified symptoms such as fatigue, sadness, and trouble sleeping.

While there has been limited research examining symptoms specific to NAFLD, efforts to examine and describe symptoms in liver disease, more broadly, has been done. The Chronic Liver Disease Questionnaire (CLDQ), which has been used to determine quality of life through the measurement symptoms in persons of all liver diseases, was developed from symptoms identified by patients with liver diseases (Younossi, Guyatt, Kiwi, Boparai, & King, 1999). Table 5 provides a comparison of symptoms reported in the present study, symptoms reported in the Kistler study, and symptoms included in the CLDQ (as an indicator of symptoms commonly found in other liver diseases). For example, the CLDQ has been used to measure health-related quality of life in persons with NAFLD citing poorer HRQOL compared to those with hepatitis B or C (Dan et al., 2007). Kistler and others (2010) found symptoms and poor health-related quality of life in children with NAFLD. Finally, this paper, a subsection of the primary author's dissertation work entitled, *Symptoms, Genetics, and HRQOL in persons with nonalcoholic fatty liver disease*, measured the presence of symptoms in persons with NAFLD (Houghton-Rahrig et al., 2011).

There are many similar symptoms across these three studies. For example, physical symptoms of fatigue or lack of energy was found in adults and children in these comparative studies (Houghton-Rahrig et al., 2011; Kistler et al., 2010; Younossi et al., 1999). Abdominal discomfort and liver ache or pain were also noted in both studies and as well as in the CLDQ. In addition, persons identified psychological symptoms, such as irritability, with similar frequencies (Houghton-Rahrig et al., 2011; Kistler et al., 2010; Younossi et al., 1999).

Limitations of study

Several limitations are acknowledged. This cross-sectional study used a small sample of 42 participants inhibiting generalizability to the population. In addition, no control group was

used to compare a symptoms experience in persons without NAFLD against those with NAFLD. Further research would benefit from the inclusion of a control group of persons without NAFLD, matched by age, gender, weight, and ethnicity, in order to minimize the effects of biases and confounding factors on understanding these relationships (Polit & Hungler, 1995).

Although all participants had a diagnosis of NAFLD, staging of NAFLD from liver biopsy was only available for a small percentage of participants, and, in some cases, these liver biopsies were conducted months to a few years prior to the present study. The lack of liver biopsy results is not uncommon in this population as liver biopsies are rarely conducted unless severe disease is suspected (Angulo, 2007). However, this limited our ability to fully compare the presence and attributes of symptoms across disease stages. In addition, the lack of liver biopsy results conducted during recruitment of the study prohibited comparison of disease stage with *PNPLA3* genotype. This experience also highlights the need for other biomarkers of disease stage. In our case, the *PNPLA3* (rs738409)-G variant was used to stratify patients based on risk of progression.

While symptoms were prevalent among our participants, we acknowledge that the reported symptoms are also commonly found in other liver diseases as noted in Table 5 by the comparison of the CLDQ, a tool used to measure quality of life in patients with liver disease (Younossi et al., 1999). While not all symptoms in this study and Kistler's study are congruent with the CLDQ, many are. Further comparative studies are needed to control for other comorbidities that may be contributing to symptoms.

While *PNPLA3* gene (rs738409) genotype did not contribute to symptoms in our small sample, it cannot be ruled out as a potential biomarker of value in studying NAFLD symptoms. We examined only one polymorphism within the *PNPLA3* gene, (rs738409) based on its prior associations with NAFLD risk; however, other genes and other polymorphisms within the *PNPLA3* gene may be associated with symptom production. In addition, a larger sample size may have provided additional power to compare the genotypes of CC, CG and GG beyond a binary comparison. To date, the *PNPLA3* gene has not been associated with symptoms, but severity of liver disease (Sookoian et al., 2009a).

Race and ethnicity were also self-reported. While self-report is common in research, this study may have benefited from ancestry genotyping testing to determine dominant race/ethnicity, especially in the multi-racial groups. Tian et al. examined the *PNPLA3* variant using ancestry genotyping as alcoholic fatty liver disease as is NAFLD, more common in the Hispanic population (Tian et al., 2010).

Medications may be a contributor to the symptoms experienced in this sample. For example, symptoms of dry mouth may be due to the administration of diuretic or allergy medications. Further study is needed to investigate the role of medications with symptoms in this population.

A larger effect size was used in the power calculation for this study. It is possible that the relationship between symptoms and the *PNPLA3* gene, (rs738409)-G allele may be weak. A larger sample size may highlight these differences. Despite these limitations, this research provides a critical and comprehensive foundational description of the symptom experience in persons with NAFLD.

A possible alternative explanation for the symptoms reported by our participants is that they are due to the presence of obesity. In our study, there was not a significant relationship between symptoms and BMI. However, the potential role of obesity and production of symptoms remains an important question. Fatty deposits in the liver are hypothesized to set

up a systemic inflammatory response that influences symptom production of “mood disorders, sleep disturbances, cognitive impairments, and sickness behaviors such as fatigue, malaise, lethargy, loss of appetite and loss of social interest” (D'Mello & Swain, 2011) [p.G750]. Higher circulating levels of TNF- α have been noted in obese persons with NASH (the inflammatory stage of NAFLD) compared to obese patients serving as controls for the study (Baranova et al., 2007). D'Mello and Swain (2011) purport that TNF- α , IL-1 and IL-6 play a role in a symptoms experience in persons with chronic liver disease and may provide an explanation for the presence of generalized, common symptoms other than liver discomfort reported by participants in this study.

In our study, 33% had liver biopsies determining all had NASH and on average, the total population experienced a mean of 12 symptoms with a higher percentage of persons experiencing some of the symptoms noted in the sickness behavior or signs of inflammation such as fatigue (59.5%) lack of energy (71.4%), difficulty concentrating (33.3%), difficulty sleeping (47.6%), lack of appetite (21.4%) and mood disorders such as feeling sad (40.4), irritable (57.2%) or nervous (38.1%). While preliminary work has been conducted in cancer populations of the role of cytokines and symptom production, (Aouizerat et al., 2009; Illi et al., 2012) further work is needed in this case to provide insight about the mechanisms underlying a symptoms experience in persons with NAFLD.

Implications for Nursing Practice and Research

Hegyvary (1993) defines symptoms as the “red flags to health” (p.146). In this population, symptoms may be triggers for health care providers to evaluate patients for the presence of NAFLD, especially persons at higher risk such as those with obesity, metabolic syndrome or diabetes. Once identified, interventions implemented in the early stages of NAFLD will reverse the disease progression. The identification of symptoms in this study suggests that persons with NAFLD may need assistance with symptom monitoring and management. Nurses are experts in the monitoring and treatment of symptoms as well as in supporting self-management of symptoms, as they promote health, manage chronic disease and treat the human response (American Nurses Association, 2010). Timely access to care in the early identification of NAFLD and treatment of symptoms in persons with chronic disease from NAFLD will promote optimal care for this population.

Further research with a larger sample size and more race/ethnic diversity is needed to determine a symptoms experience in persons with NAFLD. Research should include staging and grading of NAFLD as recommended by the American Association for the Study of Liver Disease (Chalasani et al., 2012). Longitudinal studies are needed to determine the symptoms experience along the trajectory of NAFLD from simple fatty liver disease, to NASH with and without fibrosis, liver cirrhosis, and liver cancer. Lastly, further study is needed to understand the physiological mechanisms of symptoms as charged by the National Institute of Nursing Research initiatives in order to effectively prevent, treat and manage NAFLD in all stages of disease (National Institute of Nursing Research, 2011).

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Table 1

Validity and Reliability of Instruments.

Instruments	Reliability	Validity
<i>Charlson Comorbidity Index</i> ¹	High test-retest reliability – controlling for comorbid conditions ^{2,3,4,5}	High validity- controlling for comorbid conditions and predicting mortality ^{4,5} $\chi^2 = 165$, $p < .0001$
<i>Memorial Symptom Assessment Scale</i>	High internal consistency in psychological subscale and most frequently occurring physical symptoms (Cronbach = 0.83-0.88). ⁶ Moderate internal consistency with less frequently occurring physical symptoms (Cronbach = 0.58).	High criterion with Functional Living Index (-.078) ⁶ Rand physical distress (.48) ⁶ Rand psychological distress (.80) ⁶

¹(Charlson, Szatrowski, Peterson, & Gold, 1994);

²(Birim et al., 2003);

³(Jepsen, Vilstrup, Andersen, Lash, & Sorensen, 2008);

⁴(Charlson et al., 1994);

⁵(de Groot, Beckerman, Lankhorst, & Bouter, 2003);

⁶(Portenoy et al., 1994).

Table 2

Descriptive Statistics-Demographic, Disease, and Individual Characteristics; and Symptoms Experience.

Demographic Characteristics	<i>PNPLA3</i> (rs738409) Genotype CC (N=18)	<i>PNPLA3</i> (rs738409) Genotype CG or GG (N=24)	Total Sample	<i>p-value</i>
Sex:				.403 ^c
Male, <i>n</i> , (%)	4 (9.5)	8 (19.0)	12 (28.6)	
Female, <i>n</i> , (%)	14 (33.3)	16 (38.1)	30 (71.4)	
Age, mean (SD)	43.83 (10.79)	47.04 (10.15)	45.67 (10.42)	.330 ^b
Race/Ethnicity				
• White, <i>n</i> , (%)	14 (33.3)	22 (52.4)	36 (85.7)	
• Hispanic, <i>n</i> , (%)	0 (0)	2 (4.8)	2 (4.8)	
• Black, <i>n</i> , (%)	1 (2.4)	0 (0)	1 (2.4)	
• Multi-racial, <i>n</i> , (%)	3 (7.1)	0 (0)	3 (7.1)	
• White vs. "nonwhite"				.375 ^a
Education				.474 ^c
• High school or less, <i>n</i> (%)	11 (26.2)	12 (28.6)	23 (54.8)	
• College education, <i>n</i> (%)	7 (16.6)	12 (28.6)	19 (45.2)	
Employment,				.533 ^c
• Employed <i>n</i> (%)	9 (21.4)	15 (35.7)	24 (57.1)	
• Unemployed, retired or disabled, <i>n</i> (%)	9 (21.4)	9 (21.4)	18 (42.9)	
Access to Healthcare,				.653 ^c
• Outlying areas	11 (26.1)	13 (31.0)	24 (57.1)	
• City or suburb with 2 hospitals, <i>n</i> (%)	7 (16.7)	11 (26.2)	18 (42.9)	
Disease Characteristics	<i>PNPLA3</i> (rs738409) Genotype CC (N=18)	<i>PNPLA3</i> (rs738409) Genotype CG or GG (N=24)	Total Sample	<i>p-value</i>
<i>PNPLA3</i> (rs738409) genotype				
• CC, <i>n</i> , (%)	18 (42.8)	-	18 (42.8)	-
• CG, <i>n</i> , (%)	-	17 (40.5)	17 (40.5)	-
• GG, <i>n</i> , (%)	-	7 (16.7)	7 (16.7)	-
BMI, mean (SD)	43.57 (13.24)	36.76 (6.56)	39.68 (10.41)	.034 ^b
Disease Characteristics	<i>PNPLA3</i> (rs738409) Genotype CC (N=18)	<i>PNPLA3</i> (rs738409) Genotype CG or GG (N=24)	Total Sample	<i>p-value</i>
Metabolic Syndrome, <i>n</i> (%)	7 (16.6)	7 (16.6)	14 (33.2)	.508 ^a
Waist-hip circumference ratio, mean (SD)	.919 (.073)	.941 (.076)	.932 (.075)	.337 ^b
Number of comorbid conditions, mean (SD)	2.4 (1.65)	1.75 (1.15)	2.09 (1.41)	.138 ^b
AST elevation now/past, <i>n</i> (%)	5 (12.5)	10 (24.4)	15 (36.6)	.422 ^c
ALT elevation now/past, <i>n</i> (%)	8 (19.5)	16 (39.0)	24 (58.5)	.209 ^c
Number of medications, mean (SD)	7.22 (3.90)	6.17 (3.65)	6.62 (3.75)	.374 ^b

Demographic Characteristics	<i>PNPLA3</i> (rs738409) Genotype CC (N=18)	<i>PNPLA3</i> (rs738409) Genotype CG or GG (N=24)	Total Sample	<i>p</i> -value
Individual Characteristics	<i>PNPLA3</i> (rs738409) Genotype CC (N=18)	<i>PNPLA3</i> (rs738409) Genotype CG or GG (N=24)	Total Sample	<i>p</i> -value
Prior Health Knowledge of NAFLD, <i>n</i> (%)	11 (26.2)	17 (40.5)	28 (66.7)	.508 ^c
Symptoms Experience	<i>PNPLA3</i> (rs738409) Genotype CC (N=18)	<i>PNPLA3</i> (rs738409) Genotype CG or GG (N=24)	Total Sample	
Symptoms, mean (SD)	11.67 (9.54)	12.29 (8.44)	12.02 (8.81)	.823 ^b

^aFisher's Exact;

^bIndependent t-test;

^cPearson Chi-Square;

Table 3
Symptom Frequencies vs. PNPLA3 Gene, (rs738409)-G Allele Odds Ratios

Symptom	Frequency n (%)	Number of participants with 1 or 2 copies of PNPLA3 (rs738409)-G allele reporting symptom n (%)	OR	95% CI	Fisher's Exact two-sided
Lack of energy	30 (71.4)	16 (53.3)	.571	[.141, 2.313]	.506
Pain	27 (64.3)	17 (63.0)	1.943	[.540, 6.990]	.347
Fatigue	25 (59.5)	16 (64.0)	2.000	[.570, 7.013]	.348
Feeling irritable	24 (57.2)	13 (54.2)	.752	[.217, 2.604]	.757
Worrying	22 (52.4)	13 (59.1)	1.182	[.347, 4.019]	1.000
Feeling drowsy	21 (50.0)	13 (61.9)	1.477	[.432, 5.046]	.756
Diarrhea	21 (50.0)	13 (61.9)	1.477	[.432, 5.046]	.756
Difficulty sleeping	20 (47.6)	12 (60.0)	1.250	[.367, 4.262]	.764
Feeling bloated	19 (45.2)	11 (57.9)	1.058	[.310, 3.613]	1.000
Numbness/tingling in hands/feet	18 (42.8)	10 (55.6)	.893	[.260, 3.067]	1.000
Feeling sad	17 (40.4)	8 (47.1)	.500	[.143, 1.753]	.348
Feeling nervous	16 (38.1)	9 (56.3)	.943	[.268, 3.315]	1.000
Swelling of arms or legs	16 (38.1)	10 (62.5)	1.429	[.400, 5.099]	.750
Dry mouth	15 (35.7)	8 (53.3)	.786	[.220, 2.804]	.754
Shortness of breath	15 (35.7)	10 (66.7)	1.857	[.500, 6.899]	.517
Sweats	15 (35.7)	8 (53.3)	.786	[.220, 2.804]	.754
Ache or discomfort in/below right lower rib	15 (35.7)	7 (46.7)	.515	[.143, 1.852]	.347
Difficulty concentrating	14 (33.3)	8 (57.1)	1.000	[.274, 3.656]	1.000
Cough	14 (33.3)	8 (57.1)	1.000	[.274, 3.656]	1.000
Constipation	13 (30.9)	8 (61.5)	1.300	[.342, 4.943]	.748
Problems w/sexual activity/interest	12 (28.6)	7 (58.3)	1.071	[.276, 4.154]	1.000
Itching	12 (28.6)	8 (66.7)	1.750	[.432, 7.084]	.506
Dizziness	12 (28.6)	7 (58.3)	1.071	[.276, 4.154]	1.000
Weight loss	12 (28.5)	8 (61.5)	1.300	[.342, 4.943]	.748
Nausea	11 (26.2)	5 (45.5)	.526	[.131, 2.112]	.483
Problems with urination	10 (23.8)	7 (70.0)	2.059	[.450, 9.416]	.473
Change in the way food tastes	10 (23.8)	7 (70.0)	2.059	[.450, 9.416]	.473
Changes in skin	10 (23.8)	7 (70.0)	2.059	[.450, 9.416]	.473

Symptom	Frequency <i>n</i> (%)	Number of participants with 1 or 2 copies of <i>PNPLA3</i> (rs738409)-G allele reporting symptom <i>n</i> (%)	<i>OR</i>	95% CI	Fisher's Exact two-sided
Lack of appetite	9 (21.4)	3 (33.3)	.286	[.060, 1.355]	.139
"I don't look like myself"	8 (19.0)	6 (75.0)	2.667	[.470, 15.136]	.431
Hair loss	7 (16.6)	3 (42.9)	.500	[.097, 2.584]	.438
Vomiting	5 (11.9)	2 (40.0)	.455	[.068, 3.057]	.636
Difficulty swallowing	5 (11.9)	4 (80.0)	3.400	[.346, 33.397]	.371
Mouth sores	4 (9.5)	3 (75.0)	2.429	[.231, 25.510]	.623

Note. *OR* = odds ratio; CI = confidence level. From "Symptoms, Genetics, and Health-Related Quality of Life in Persons with Nonalcoholic Fatty Liver Disease" by L. Houghton-Rahrig, D.L. Schutte, J.I. Fenton, B.A. Given, N.G. Hord., A. Von Eye, 2011, (Dissertation). Copyright 2011 by Lori Houghton-Rahrig.

Table 4
MSAS Subscales and significant predictors of symptom attribute

MSAS Subscale	Model $df1 = 15, df2 = 25$	Predictors (coding)	Beta	p value
TMAS	$F=2.609, p=.016$	White (1) vs. nonwhite (0) ^a	-.812	.003
MSAS-GDI	$F=3.331, p=.004$	White (1) vs. nonwhite (0) ^a	-.954	.002
		Unemployed, retired, disabled (1) vs. employed (0)	.529	.036
MSAS-PHYS	$F=2.726, p=.013$	White (1) vs. nonwhite (0) ^a	-.983	<.001
		Health Knowledge of NAFLD prior to recruitment into study (1 = Yes)	.448	.036
MSAS-PSYCH	$F=2.944, p=.008$	White (1) vs. nonwhite (0) ^a	-.983	.003
		Unemployed, retired, disabled (1) vs. employed (0)	.945	.006

^aThe term *white* refers to all Caucasian participants. The term *nonwhite* refers to participants of all other races, including African American, Hispanic, and multiracial participant.

Table 5
Comparison of Symptoms of Chronic Liver Disease with Symptoms Found in Children and Adults with NAFLD

Symptoms found in development of Chronic Liver Disease Questionnaire (%)	Symptoms found in children with NAFLD (%) Symptom mean= 5	Symptoms, Genetics, and HRQOL in Persons with NAFLD (%) Symptom mean=12
Fatigue domain		
Tiredness or fatigue (80)	Fatigue (68)	Fatigue (59.5)
Sleepiness during the day (80)		Feeling drowsy (50.0)
Decreased strength (69)		
Decreased level of energy (81)		Lack of energy (71.4)
Felt Drowsy (63)		
Abdominal pain domain		
[Feeling bloated] ^a (66)	Swelling abdomen (20)	Feeling bloated (45.2)
Abdominal bloating (58)	Liver pain (41)	Ache/discomfort rt lower rib area (35.7)
Abdominal discomfort (55)	Diarrhea (35)	Diarrhea (50) Constipation (30.9)
Emotional function		
Anxious (69)		Feeling nervous (38.1)
Unhappy		Difficulty sleeping (47.6)
Irritable (55)	Irritability (73)	Feeling irritable (57.2)
Difficulty sleeping (61)		Difficulty sleeping (47.6)
Mood swings (52)		
Inability to fall asleep at night (58)		
Felt depressed (56)		Feeling sad (40.4)
Problems concentrating (<i>not available</i>)	Trouble concentrating (55)	Difficulty concentrating (33.3)
Systemic symptoms		
Bodily pain	Headache (60)	Pain (64.3)
Shortness of breath (53)		Shortness of breath (35.7)
Muscle cramps (56)	Muscle aches/cramps (53)	
Dry mouth (61)		Dry mouth (35.7)
Itching (53)		Itching (28.6)
		Numbness/tingling in hands/feet (42.8)
	Swelling ankles (15)	Swelling of arms/legs (38.1)
		Sweats (35.7)
		Cough (33.3)
		Dizziness (28.6)
		Problems with sexual activity/interest (28.6)
		Weight loss (28.5)
		Problems with urination (23.8)
	Nausea (50)	Nausea (26.2)
		Vomiting (11.9)
		Changes in skin (23.8)
		"I don't look like myself" (19.0)

Symptoms found in development of Chronic Liver Disease Questionnaire (%)	Symptoms found in children with NAFLD (%) Symptom mean= 5	Symptoms, Genetics, and HRQOL in Persons with NAFLD (%) Symptom mean=12
		Hair loss (16.6)
		Mouth sores (9.5)
Activity		
Unable to eat as much as preferred (56)		
Trouble lifting or carrying heavy Objects (53), (55)		
Limitation of diet		
Worry		Worrying (52.4)
Concern about liver disease impact on family (64)		
Worried symptoms will develop into major problems (73)		
Worried conditions will get worse (83)		
Worried never going to feel better (52)		
Concerned about transplant availability (55)		

Note. NAFLD = nonalcoholic, fatty liver disease. Adapted from Younossi, Z. M., Guyatt, G., Kiwi, M., Boparai, N., & King, D. (1999). Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut*, 45(2), 295-300. Adapted from Kistler, K. D., Molleston, J., Unalp, A., Abrams, S. H., Behling, C., & Schwimmer, J. B. (2010). Symptoms and quality of life in obese children and adolescents with non-alcoholic fatty liver disease. *Alimentary Pharmacology & Therapeutics*, 31(3), 396-406. From "Symptoms, Genetics, and Health-Related Quality of Life in Persons with Nonalcoholic Fatty Liver Disease" by L. Houghton-Rahrig, D.L. Schutte, J.I. Fenton, B.A. Given, N.G. Hord., A. Von Eye, 2011, (Dissertation). Copyright 2011 by Lori Houghton-Rahrig.

^aSymptom combined with others in final Chronic Liver Disease Questionnaire.